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Frequent Physical Activity May not Reduce Vascular Disease Risk as Much as Moderate Activity: Large Prospective Study of UK Women

Running title: *Armstrong et al.; Physical activity and vascular disease in UK women*

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Abstract

Background - While physical activity has generally been associated with reduced risk of vascular disease, there is limited evidence about the effects of the frequency and duration of various activities on incidence of particular types of vascular disease.

Methods and Results - In 1998, on average, 1.1 million women without prior vascular disease reported their frequency of physical activity and many other personal factors. Three years later, they were asked about hours spent doing walking, cycling, gardening and housework. Women were followed by record linkage to NHS cause-specific hospital admissions and death records. Cox regression was used to calculate adjusted relative risks for first vascular events in relation to physical activity. During an average of 9 years follow-up, 49,113 women had a first coronary heart disease event (CHD), 17,822 had a first cerebrovascular event, and 14,550 had a first venous thromboembolic event (VTE). Compared to inactive women, those reporting moderate activity had significantly lower risks of all three conditions ($p<0.001$ for each). However, women reporting strenuous physical activity daily had higher risks of CHD ($p=0.002$), cerebrovascular disease ($p<0.001$) and VTE ($p<0.001$) than those reporting doing such activity 2-3 times per week. Risks did not differ between hemorrhagic and ischemic stroke, or between VTE with or without pulmonary embolism.

Conclusions - Moderate physical activity is associated with a lower risk of CHD, VTE and cerebrovascular disease than inactivity. However, among active women there is little to suggest progressive reductions in risk of vascular diseases with increasing frequency of activity.

Key words: Coronary disease, Cerebrovascular disease, Venous Thromboembolism, Exercise

Introduction

Physical activity has been associated with a reduced risk of coronary heart disease (CHD) [1-4] and cerebrovascular disease[1,4-6] in women. The relationship is less clear when risk is examined separately for hemorrhagic and ischemic stroke,[7, 8] and there are relatively few reports on the relationship with venous thromboembolism (VTE).[9-13] Few previous studies have had sufficient power to examine reliably how risk is related to the frequency or duration of overall and specific physical activities, especially for stroke and VTE. It is also unclear whether some of the reported inverse association between vascular disease and physical activity could represent "reverse causation" due to pre-clinical disease, in that early symptoms of vascular disease may cause some people to reduce their activities.

We describe here the relationships of frequency, duration and type of physical activity with incident coronary heart disease, cerebrovascular disease (overall and separately for hemorrhagic and ischemic stroke), and VTE (overall and separately for those with and without pulmonary embolism), excluding the first 4 years of follow-up from recruitment into the study, in order to limit the possible effects of reverse causation due to pre-clinical disease.

Methods

Data collection

From 1996-2001, women attending National Health Service (NHS) breast cancer screening clinics in England and Scotland were recruited into the Million Women Study, a prospective cohort study. In total, 1.3 million women aged 50 to 64 gave their written consent to participate in the study and completed a recruitment questionnaire including questions on: physical activity, anthropometry, lifestyle, health, and socio-demographic factors (see http://www.millionwomenstudy.org). Further details of the Million Women Study design and

methods are available elsewhere[14]. The Anglia and Oxford Multi-Centre Research Ethics Committee granted permission to conduct the study.

Each woman was linked to NHS data on cause-specific deaths, and hospital admissions (including inpatient and day-case admissions) from the Hospital Episodes Statistics for England[15] and Scottish Morbidity Records in Scotland,[16] using their unique NHS identification number and other personal details. Information on dates and diagnoses related to each hospital admission or death was provided, coded to the World Health Organisation's International Classification of Diseases, 10th revision (ICD-10).[17] For these analyses, incident cases were defined as the first hospital record or death from CHD (ICD 10: I20 - I25), cerebrovascular disease (ICD 10: I60 – I69), or VTE (Incorporating pulmonary embolism, ICD 10: I26; deep vein thrombosis and other venous thrombosis without pulmonary embolism, ICD 10: I80 - I82) occurring after recruitment into the study. In each specific analysis of interest (of coronary heart disease, cerebrovascular disease, or venous thromboembolism), subjects were not censored at the occurrence of a different vascular disease diagnosis. Separate analyses were done for subarachnoid haemorrhage (ICD 10: I60), intracerebral haemorrhage (I61), cerebral infarction (I63), pulmonary embolism (I26), and deep vein thrombosis and other venous thrombosis without pulmonary embolism (I80-I82). In a validation study, 93% of women with a hospital admission for ischemic heart disease, cerebrovascular disease or VTE had this diagnosis confirmed by their general practitioner (who hold full clinical records of all people registered with the NHS).[18]

Measures of Physical Activity

Measures of physical activity from recruitment (baseline) provided information on self-reported frequency of strenuous and any physical activity (average 9 years follow-up per

woman). At baseline, all women were asked “How often do you do any strenuous exercise? (that is, enough to cause sweating or a fast heart beat)”, and an additional question was added after the first 9% of participants had completed the questionnaire: “How often do you do any exercise?”. Women could respond to each question with one of six options: ‘Rarely/never’, ‘less than once a week’, ‘once a week’, ‘2-3 times a week’, ‘4-6 times a week’, ‘every day’.

Approximately 3 years after recruitment, study participants were sent a resurvey questionnaire, asking: “About how many hours each week do you spend doing: housework, gardening, walking, cycling, any work or exercise causing sweating or a fast heartbeat”, asking separately about summer and winter durations for each activity, except for housework. Thus, measures of physical activity from the 3-year resurvey (average 9 years of follow-up per woman, no follow-up excluded) provided information on the volume of specific activities. These questions were structured using validated, session-based measures of physical activity questions from the International Physical Activity Questionnaire[19] and the Active Australia Survey.[20] The numbers of hours spent on these specific activities were strongly associated with responses to the simple questions on the frequency of strenuous and any activity asked at baseline.[21]

We report excess MET-hours of activity, representing the energy expenditure associated with activity above the baseline metabolic levels of an inactive person.[22] Excess MET-hours for each activity were calculated by subtracting one from the multiplier listed for the activity in Ainsworth's compendium of physical activities,[23] and multiplying this MET value by the number of hours reported for the activity (for detailed methods see[21]). Excess MET-hours per week were calculated by summing MET-hours for all physical activities reported at the 3-year resurvey: walking, gardening, cycling, strenuous activity, and housework.

Statistical Analyses

We excluded from this analysis all women who had invasive cancer (3%), or a hospital record of CHD, cerebrovascular disease, or VTE (1%), prior to recruitment. We also excluded those self-reporting having had or being treated for heart disease, stroke, thrombosis or diabetes (12%) at recruitment, and those with missing information on strenuous physical activity (4%). Following these exclusions, 1,119,239 women remained for analyses from baseline, and 497,857 women remained for analyses of specific activities from the 3-year resurvey.

Reliable hospital data were available for women recruited in Scotland from January 1st, 1981, and for women recruited in England from April 1st, 1997. For the main analyses, follow-up was calculated from four years after recruitment into the study or four years after April 1st 1997, for the 5% of women recruited in England prior to this date. Follow-up continued until whichever came first of: the date of the first hospital admission for the disease of interest for the given analysis (ie. incident coronary heart disease, incident cerebrovascular disease, or incident venous thromboembolism); the date of death; the date of emigration or other loss to follow-up; or the end of follow-up. The end of follow-up was March 31, 2012 for participants in England, and December 31, 2008 for participants in Scotland.

Characteristics of participants in relation to categories of strenuous physical activity at baseline, and of cycling, walking, gardening and housework three years later, were summarized with means and standard deviations, or numbers and proportions.

Cox regression models with age as the underlying time variable were used to estimate relative risks and 95% confidence intervals for incident coronary heart disease, cerebrovascular disease, and VTE, according to different measures of overall and specific physical activities. Sensitivity analyses examining the effect of excluding the first 4 years of follow-up were conducted to assess the magnitude of potential bias due to reverse causation. Because some previous reports have suggested that there may be differences between the risk relationships for different pathological types of stroke, [6, 24, 25] we estimated relative risks and 95% confidence intervals separately for subarachnoid haemorrhage, intracerebral haemorrhage, and cerebral infarction. We also separately examined relative risks and 95% confidence intervals for VTE subtypes (pulmonary embolism; deep vein thrombosis and other venous thrombosis without pulmonary embolism). We used chi-squared tests for heterogeneity of trends to test for differences between the risk relationships for cerebrovascular and VTE subtypes.

The Cox regression models were stratified by socioeconomic status (quintiles using the Townsend index[26]) and recruitment region (ten regions), and adjusted for BMI (<20, 20.0-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, ≥30.0 kg/m^2), smoking status (current, past, never) and alcohol consumption (0,0.1-1.9,3-6.9,7-14.9, ≥15 drinks per week), each treated as time-dependant co-variates according to three age bands (<60,60-64,65+). An additional category was created for each adjustment variable for women with missing data (usually <2%). To allow for valid comparisons between any two groups when more than two categories were compared, hazard ratios (called relative risks here) were treated as floated absolute risks,[27] and are presented with the corresponding group-specific confidence intervals (CIs) for the log risk, which allow relative risks to be compared between any two categories, even if neither is the reference group. Conventional confidence intervals are given in the text for explicit

comparisons between two categories. Proportional hazards testing using Schoenfeld residuals showed that the models did not violate the proportional hazards assumption.

Subgroup analyses were conducted to assess whether the risk relationships differed by major lifestyle factors including BMI, smoking, and socioeconomic status. Heterogeneity of risk relationships across sub groups of each of these factors was assessed using likelihood ratio tests.

The STATA statistical package (version 12.0, Statacorp, Texas) was used for all analyses. All statistical tests were two-sided and statistical significance was assessed at the 0.05 level.

Results

The characteristics of women included in these analyses are presented in Tables 1 and Supplemental Table 1. At baseline women were aged 55.9 (SD 4.8) years on average, with a mean BMI of 26.0 (SD 4.5) kg/m^2. With increasing frequency of baseline strenuous and any physical activity, there was a progressive decrease in mean weight, mean BMI and proportion treated for hypertension, and an increase in mean MET-hours per week of activity reported at 3-year follow-up (Table 1). Three years later, almost half a million women reported hours spent doing various activities. Those who reported doing gardening or walking at the 3-year resurvey had lower mean BMI and weight at baseline, and a smaller percentage were current smokers, than women who were less active in these specific physical activities (Supplemental Table 1). However, there was little difference in the characteristics of women by the reported time doing housework. For activities other than housework, a greater proportion of inactive women reported being treated for hypertension at baseline.

During an average of 9 years (median = 9 years; interquartile range 8-10 years) of follow-up (after excluding the first 4 years of follow-up), there were 49,113 women with incident coronary heart disease, 17,822 with incident cerebrovascular disease (1774 subarachnoid haemorrhage, 1791 intracerebral haemorrhage, and 5993 cerebral infarction), and 14,550 with incident VTE (7712 venous thrombosis without pulmonary embolus, 7013 pulmonary embolism). Women aged 55 to 80 years had an absolute risk of 610 per 100,000 per year for CHD, 252 per 100,000 per year for cerebrovascular disease, and 173 per 100,000 per year for VTE. From the 3-year resurvey, there were 20,208 incident cases of coronary heart disease, 6815 incident cases of cerebrovascular disease, and 5767 incident cases of VTE with an average follow-up of 9 years (median 9 years; interquartile range 8-11), no follow-up excluded.

The frequency of strenuous or any physical activity at baseline was associated with a reduced risk of subsequent coronary heart disease, cerebrovascular disease, and VTE, which remained after adjustment for BMI-by-age, smoking-by-age, alcohol-by-age and stratification for socioeconomic status and region of recruitment (Table 2). Figure 1 shows, however, that there was not a progressive decrease in risk with increasing frequency of strenuous or any physical activity. Risk of cerebrovascular disease and VTE were significantly increased in women reporting activity daily, compared to those reporting activity 2-3 times per week ($P < 0.001$). For CHD this comparison was significantly increased for strenuous physical activity ($P=0.002$) but not for any physical activity ($P=0.8$). A sensitivity analysis conducted without dropping the first four years of follow-up, showed slightly greater differences between active and inactive women for each of the three vascular disease types, suggesting that there may well be some bias due to reverse causation (Supplemental Table 2).

Subgroup analyses within categories of BMI (Supplemental Tables 3-5) showed that the apparent benefits of physical activity were greatest amongst lean women for CHD ($P_{for\ heterogeneity}<0.001$ for strenuous activity; $P_{for\ heterogeneity}=0.007$ for any activity) and cerebrovascular disease ($P_{for\ heterogeneity}=0.009$, and $P_{for\ heterogeneity}=0.03$, respectively). There was also evidence that associations of CHD with physical activity differed by smoking status ($P_{for\ heterogeneity}<0.001$, and $P_{for\ heterogeneity}=0.003$, respectively), and was greatest in past smokers. There was no significant heterogeneity by socioeconomic status ($P_{for\ heterogeneity}\geq 0.1$). Results for VTE subgroup analyses showed no strong evidence of heterogeneity between categories of BMI, smoking and socioeconomic group.

The proportions of medication for vascular disease used within each activity group differed for all medication types except anticoagulants (Supplemental Table 6). In general the more active women used less medication, consistent with the higher rates of hypertension and hypercholesterolemia at baseline (Table 1).

Physical activity had similar associations with the different pathological types of stroke (subarachnoid haemorrhage, intracerebral haemorrhage, and cerebral infarction; test for heterogeneity of trend across subtypes: P = 0.5 for strenuous activity, and P = 0.3 for any physical activity, Table 3). Associations with physical activity were also similar for the different pathological types of VTE (pulmonary embolism, and venous thrombosis without pulmonary embolism; P for heterogeneity of trend across subtypes: P = 0.6 for strenuous activity, and P = 0.9 for any physical activity, Table 4).

In comparison to the reference groups for the specific activities (up to 1 hour per week walking; 0 hours per week gardening or cycling, and up to 3 hours per week doing

housework), women reporting longer durations of these activities tended to have a lower risk of coronary heart disease, cerebrovascular disease, and VTE (Table 5). For cycling, which was infrequent in this cohort, this reduction was only clear for coronary heart disease, while for housework the reduction was only clear for cerebrovascular disease and VTE. For an aggregate of these specific physical activities, measured as excess MET-hours per week, the main difference in the risk of coronary heart disease, cerebrovascular disease and VTE was between the least active group (<40 excess MET-hours per week) and the other groups, with little evidence of progressive reductions in risk with more activity. Sensitivity analyses excluding the first 4 years of follow-up showed a small attenuation in the strength of the associations, but results were similar.

Discussion

Results from this prospective study of 1.1 million UK women showed that different types of physical activity were associated with lower incidence of coronary heart disease, cerebrovascular disease, and venous thromboembolism than inactivity. Overall, the main difference in risk was between those doing some activity versus none, with the lowest risks being observed among women doing moderate amounts of activity. These associations were evident for different pathological types of stroke and of VTE, and across analyses using different measures of physical activity, including frequency of any or strenuous activity, excess metabolic equivalents of energy expended (METs), and durations of specific types of activity. Among active women, there was little evidence of progressive reductions in risk with more frequent activity, and even an increase in risk for CHD, cerebrovascular disease, and VTE in the most active group.

For CHD in middle-aged women, our findings were generally consistent with results from meta-analyses that are mainly based on prospective studies, showing benefit from some physical activity.[1-4] However, quantification of risk with high levels of activity in these meta-analyses was limited by varying definitions across studies. Some individual studies in these meta-analyses reported an upturn in risk at higher activity levels, as found here.

Previous studies of the relationship between physical activity and cerebrovascular disease in women have indicated that women who are more active may be at lower risk than those who are less active. Results from meta-analyses have shown significantly lower overall risks of stroke among women with higher compared to lower levels of physical activity.[1,4-6] However, published results on associations with specific pathological types of stroke (ischaemic or hemorrhagic) had limited statistical power, and we found no difference here, with larger numbers of cases than had been reported previously. [6,25]

Immobilization is thought to increase the risk of VTE,[28] but there are few reports on the relationship between VTE and usual physical activity in women. One prospective study[9] reported no association between incident idiopathic pulmonary embolism and physical activity, while two others[10, 11] reported no significant associations between physical activity and deep vein thrombosis or pulmonary embolism, but the lack of significant differences may have resulted from small sample sizes. Two retrospective studies reported that sports participation and vigorous physical activity were associated with a lower risk of venous thromboembolism, identified through anticoagulation clinics,[12] or through hospital admissions and insurance claims.[13]

There are many ways in which exercise might reduce the risk of developing CHD, cerebrovascular disease and VTE. Risk factors such as hypertension, body weight, and insulin resistance are improved with physical activity.[29] Physical activity also leads to increases in high density lipoprotein levels,[29] improvements in endothelial function,[30] decreases in systemic inflammation which is thought to play a key role in atherosclerosis pathophysiology,[31] reductions in fibrinogen which may lead to decreased plasma viscosity,[30, 32, 33] and reductions in platelet aggregation.[30, 34] Muscular activity in the lower limbs also promotes venous return.[35, 36] Each of these mechanisms may play a role in the observed association of moderate levels of activity with lower risk of hospital admission for vascular diseases. However, they do not suggest an explanation for the apparent upturn in risk at higher activity levels associated with some vascular outcomes and measures of physical activity. In our data, active women had better vascular disease risk profiles for BMI and smoking than inactive women (Table 1 and Table 2), although women who participated in daily strenuous exercise had a slightly higher mean BMI than women who exercised less frequently, and a similar prevalence of smoking to women who were inactive. Our analyses adjusted for BMI, smoking, and for alcohol consumption, but residual confounding could possibly partly explain the observation that those in the highest physical activity groups had the same or greater risk of vascular diseases as those taking moderately frequent physical activity. It has been suggested that extreme endurance exercise may be detrimental to cardiovascular health,[37] however the degree to which this may be relevant to the general population is less clear. A recent prospective study of men and women aged 44 years on average at baseline, suggested a U-shaped association between running frequency and cardiovascular mortality.[38] While the lowest risk appeared to be among those reporting running three times per week, the confidence intervals were large.

The main strengths of this study include its prospective design, the large size, and the virtually complete follow-up for hospital admissions for vascular disease in the cohort. The diagnostic reliability of hospital records for the conditions studied here is high.[18] Incident cases of coronary heart disease, cerebrovascular disease, or VTE not resulting in a day-case or overnight admission, and so not included in this study, tend to be less severe than those admitted to hospital and our results may not be generalisable to such cases.

We excluded the first four years of follow-up in our main analyses, to minimise bias by reverse causation, whereby individuals with pre-clinical disease might become less active because of early symptoms of disease. Such a bias could exaggerate the differences in risk between groups with higher and lower physical activity,[39,40] and our sensitivity analyses (including the first four years of follow-up), suggest that this was happening. Objective measures of physical activity (eg. actigraphy) were not available for comparison with the questionnaire data. However, resurvey questions were based on physical activity measures used in the International Physical Activity Questionnaire[19] and the Active Australia Survey.[20] Physical activity behaviours of subjects may change over time,[41-45] but we have demonstrated that the self-reported hours of physical activity and corresponding excess MET-hours at resurvey were positively associated with the frequency of any and of strenuous activity reported at recruitment.[21] Estimated mean excess MET-hours for strenuous activity at resurvey increased with increasing frequency of strenuous activity reported at recruitment. Similarly, mean excess MET-hours estimated from an aggregate of activities reported at resurvey increased with reported frequency of any activity at baseline. Overall, different self-reported measures of physical activity agreed well between the two surveys, in terms of their ability to rank women according to physical activity level.

Our findings indicate that moderate levels of physical activity are associated with lower risks of vascular diseases than inactivity. However, among active women there was little to suggest further reductions in risk with greater levels of activity.

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Table 1. Characteristics of women in the Million Women Study according to frequency of strenuous and any physical activity[a], reported at recruitment into the study.

	Strenuous Exercise					Any Exercise					All Women
	Rarely/ never (inactive)	**Up to once per week**	**2-3 times per week**	**4-6 times per week**	**daily**	**Rarely/ never (inactive)**	**Up to once per week**	**2-3 times per week**	**4-6 times per week**	**daily**	
Characteristics at baseline	n=530,674	n=348,537	n=168,734	n=35,560	n=35,734	n=213,100	n=244,408	n=240,835	n=89,968	n=226,551	n=1,119,239
Mean age at recruitment, years (SD)	56.2 (4.9)	55.6 (4.7)	55.7 (4.7)	55.6 (4.7)	55.8 (4.6)	55.8 (4.8)	55.4 (4.6)	56.0 (4.8)	56.2 (4.9)	56.3 (4.9)	55.9 (4.8)
Mean height, cm (SD)	161.6 (6.7)	162.4 (6.6)	162.5 (6.5)	162.6 (6.6)	162.2 (6.9)	161.2 (6.8)	162.0 (6.6)	162.3 (6.5)	162.6 (6.5)	162.3 (6.7)	162.0 (6.7)
Mean weight, kg (SD)	69.4 (13.1)	67.8 (11.5)	66.6 (10.9)	65.2 (10.6)	66.1 (11.7)	70.6 (14.0)	69.5 (12.3)	67.5 (11.3)	66.1 (10.7)	66.4 (11.4)	68.2 (12.2)
Mean BMI, kg/m^2 (SD)	26.6 (4.8)	25.7 (4.2)	25.2 (4.0)	24.7 (3.8)	25.2 (4.3)	27.2 (5.2)	26.5 (4.5)	25.7 (4.1)	25.0 (3.9)	25.2 (4.2)	26.0 (4.5)
Mean alcohol, grams/day (SD)	5.4 (7.5)	6.3 (7.4)	7.2 (8.0)	7.7 (8.7)	5.7 (8.1)	5.1 (7.5)	5.7 (7.1)	6.6 (7.6)	7.5 (8.3)	6.1 (7.9)	6.0 (7.6)
Mean METs, MET-hours/wk (SD)[c]	59.9 (42.8)	66.5 (41.6)	76.1 (45.7)	88.3 (53.5)	99.2 (72.3)	58.1 (45.4)	59.5 (40.6)	66.8 (40.8)	73.0 (42.7)	79.3 (52.3)	66.9 (45.3)
Current Smoker (%)	24.8	15.5	13.7	15.2	25.6	29.2	18.2	14.8	13.8	21.3	20.0
Never Smoker (%)	48.5	56.6	54.9	53.4	48.2	44.7	53.8	55.2	56.4	51.9	52.1
Socioeconomic status: Lowest fifth (%)	23.4	13.9	13.1	13.6	20.1	28.3	16.8	14.5	13.1	18.0	18.5
Treated for hypertension (%)	15.7	12.6	11.6	10.4	11.6	16.0	14.0	13.5	12.3	12.7	13.8
Treated for hyperlipidemia(%)	2.8	2.4	2.3	2.2	2.3	2.7	2.5	2.7	2.5	2.4	2.6
Women with incident vascular disease [b]											
Coronary heart disease (n)	27,770	12,757	5820	1201	1565	11,954	9990	9234	2996	9282	49,113
Cerebrovascular disease (n)	10,079	4491	2125	493	634	4207	3427	3189	1245	3704	17,822
Venous thromboembolism (n)	7925	3989	1711	394	531	3372	2993	2609	919	2966	14,550

[a] Women with missing values were excluded when calculating the means or percentages for that given variable

[b] An average of 9 years (median=9 years; interquartile range 8-10 years) follow-up per woman, after dropping the first 4 years of follow-up

[c] MET-hours were calculated from first resurvey (3-year follow-up) and therefore only include data from 497,857 women

Table 2. Relative risks (RR) and 95% group specific confidence intervals (gsCI) of incident vascular diseases, in women in relation to strenuous and any physical activity from baseline, excluding the first 4 years of follow-up

	CORONARY HEART DISEASE			CEREBROVASCULAR DISEASE			VENOUS THROMBOEMBOLISM		
	Incident cases/ participants	**Minimally adjusted[a]**	**Fully adjusted[b] RR (95% gsCI[c])**	**Incident cases/ participants**	**Minimally adjusted[a]**	**Fully adjusted[b] RR (95% gsCI[c])**	**Incident cases/ participants**	**Minimally adjusted[a]**	**Fully adjusted[b] RR (95% gsCI[c])**
Strenuous activity	n=1,094,327			n=1,103,156			n=1,102,479		
Rarely/never (inactive)	27,770/516,035	1.00	1.00 (0.99 – 1.01)	10,079/521,292	1.00	1.00 (0.98 – 1.02)	7925/520,964	1.00	1.00 (0.98 – 1.02)
At most once per week	12,757/342,455	0.75	0.84 (0.83 – 0.85)	4491/344,650	0.75	0.83 (0.80 – 0.85)	3989/344,429	0.81	0.90 (0.87 – 0.92)
2-3 times per week	5820/165,923	0.71	0.81 (0.79 – 0.83)	2125/166,873	0.72	0.81 (0.78 – 0.84)	1711/166,786	0.71	0.83 (0.79 – 0.87)
4-6 times per week	1201/34,967	0.69	0.80 (0.76 – 0.85)	493/35,141	0.80	0.87 (0.80 – 0.95)	394/35,112	0.77	0.92 (0.83 – 1.01)
daily	1565/34,947	0.86	0.89 (0.84 – 0.93)	634/35,200	0.97	0.96 (0.89 – 1.04)	531/35,188	1.00	1.08 (0.99 – 1.17)
$P_{for\ heterogeneity}$			< 0.001			< 0.001			< 0.001
Any activity	n=992,228			n=1,000,316			n=999,708		
Rarely/never (inactive)	11,954/206,418	1.00	1.00 (0.98 – 1.02)	4207/208,863	1.00	1.00 (0.97 – 1.03)	3372/208,707	1.00	1.00 (0.97 – 1.04)
At most once per week	9990/239,540	0.78	0.87 (0.85 – 0.88)	3427/241,440	0.77	0.87 (0.84 – 0.90)	2993/241,206	0.81	0.89 (0.86 – 0.92)
2-3 times per week	9234/236,258	0.71	0.84 (0.82 – 0.85)	3189/237,858	0.69	0.80 (0.77 – 0.83)	2609/237,763	0.70	0.83 (0.79 – 0.86)
4-6 times per week	2996/88,381	0.62	0.75 (0.73 – 0.78)	1245/88,878	0.71	0.83 (0.79 – 0.88)	919/88,843	0.66	0.82 (0.76 – 0.87)
daily	9282/221,631	0.74	0.83 (0.82 – 0.85)	3704/223,277	0.82	0.88 (0.86 – 0.91)	2966/223,189	0.82	0.96 (0.93 – 1.00)
$P_{for\ heterogeneity}$			< 0.001			< 0.001			< 0.001

[a] Stratified by SES and Region
[b] Adjusted for BMI-by-age, smoking-by-age, alcohol-by-age and stratified by SES and Region
[c] gsCI = group specific confidence interval for RR

Table 3. Relative risks (RR) and 95% group specific confidence intervals (gsCI) of incident stroke pathological subtypes, in women, in relation to strenuous and any physical activity

	SUBARACHNOID HAEMORRHAGE (ICD10: I60)			INTRACEREBRAL HAEMORRHAGE (ICD10: I61)			CEREBRAL INFARCTION (ICD10: I63)			
	Incident cases	**Minimally adjusted[a]**	**Fully adjusted[b] RR (95% gsCI[c])**	**Incident cases**	**Minimally adjusted[a]**	**Fully adjusted[b] RR (95% gsCI[c])**	**Incident cases**	**Minimally adjusted[a]**	**Fully adjusted[b] RR (95% gsCI[c])**	P *for heterogeneity of trends*[d]
Strenuous activity										0.5
Rarely/never (inactive)	954	1.00	1.00 (0.93 – 1.07)	962	1.00	1.00 (0.94 – 1.07)	3361	1.00	1.00 (0.96 – 1.04)	
At most once per week	446	0.73	0.82 (0.75 – 0.90)	490	0.83	0.87 (0.79 – 0.95)	1579	0.79	0.88 (0.84 – 0.92)	
2-3 times per week	262	0.89	1.01 (0.89 – 1.14)	219	0.76	0.77 (0.68 – 0.88)	700	0.72	0.81 (0.75 – 0.88)	
4-6 times per week	50	0.80	0.87 (0.66 – 1.14)	50	0.83	0.81 (0.61 – 1.07)	157	0.77	0.86 (0.74 – 1.01)	
daily	62	0.96	0.91 (0.71 – 1.16)	70	1.11	1.05 (0.83 – 1.33)	196	0.90	0.92 (0.80 – 1.05)	
P for heterogeneity[e]			0.009			0.003			< 0.001	
Any activity										0.3
Rarely/never (inactive)	411	1.00	1.00 (0.90 – 1.11)	364	1.00	1.00 (0.90 – 1.11)	1407	1.00	1.00 (0.95 – 1.06)	
At most once per week	352	0.78	0.89 (0.80 – 0.99)	337	0.85	0.91 (0.82 – 1.02)	1169	0.80	0.89 (0.84 – 0.94)	
2-3 times per week	340	0.77	0.90 (0.81 – 1.00)	324	0.79	0.83 (0.74 – 0.93)	1077	0.70	0.82 (0.77 – 0.87)	
4-6 times per week	118	0.72	0.83 (0.69 – 1.00)	151	0.96	0.99 (0.84 – 1.16)	408	0.70	0.83 (0.76 – 0.92)	
daily	353	0.84	0.87 (0.78 – 0.97)	394	0.99	0.98 (0.89 – 1.09)	1250	0.83	0.91 (0.86 – 0.97)	
P for heterogeneity[e]			0.3			0.1			< 0.001	

[a]Stratified by SES and Region, excluding the first 4 years of follow-up
[b]Adjusted for BMI-by-age, smoking-by-age, alcohol-by-age and stratified by SES and Region, excluding the first 4 years of follow-up
[c]gsCI = group specific confidence interval for RR
[d]$P_{for\ heterogeneity\ of\ trends}$ = for heterogeneity of the trend comparing across different pathological types of cerebrovascular disease
[e]$P_{for\ heterogeneity}$ = for heterogeneity across categories of each physical activity

Table 4. Effect of adjustment for various factors on the relative risks of incident venous thromboembolism pathological sub-types, in women, in relation to strenuous and any physical activity

	PULMONARY EMBOLISM (ICD10: I26)			VENOUS THROMBOSIS (ICD10: I80-I82)			
	Incident cases	**Minimally adjusted[a]**	**Fully adjusted[b] RR (95% gsCI[c])**	**Incident cases**	**Minimally adjusted[a]**	**Fully adjusted[b] RR (95% gsCI[c])**	$P_{for\ heterogeneity\ of\ trends}$[d]
Strenuous activity							0.6
Rarely/never (inactive)	3800	1.00	1.00 (0.97 – 1.03)	4226	1.00	1.00 (0.97 – 1.03)	
At most once per week	1918	0.81	0.90 (0.86 – 0.94)	2113	0.80	0.89 (0.85 – 0.93)	
2-3 times per week	845	0.73	0.85 (0.80 – 0.91)	885	0.69	0.80 (0.75 – 0.86)	
4-6 times per week	206	0.84	1.00 (0.87 – 1.15)	191	0.70	0.84 (0.73 – 0.97)	
Daily	244	0.95	1.03 (0.91 – 1.17)	297	1.05	1.13 (1.01 – 1.27)	
$P_{for\ heterogeneity}$[e]			< 0.001			< 0.001	
Any activity							0.9
Rarely/never (inactive)	1605	1.00	1.00 (0.95 – 1.05)	1808	1.00	1.00 (0.95 – 1.05)	
At most once per week	1468	0.84	0.92 (0.88 – 0.97)	1561	0.79	0.87 (0.82 – 0.91)	
2-3 times per week	1256	0.71	0.83 (0.79 – 0.88)	1377	0.70	0.82 (0.77 – 0.86)	
4-6 times per week	455	0.67	0.84 (0.77 – 0.92)	472	0.64	0.79 (0.72 – 0.86)	
daily	1433	0.82	0.97 (0.92 – 1.02)	1577	0.83	0.96 (0.92 – 1.01)	
$P_{for\ heterogeneity}$[e]			< 0.001			< 0.001	

[a]Stratified by SES and Region, excluding the first 4 years of follow-up
[b]Adjusted for BMI-by-age, smoking-by-age, alcohol-by-age and stratified by SES and Region, excluding the first 4 years of follow-up
[c]gsCI=group specific confidence interval for RR
[d]$P_{for\ heterogeneity\ of\ trends}$=for heterogeneity of the trend comparing across different pathological types of cerebrovascular disease
[e]$P_{for\ heterogeneity}$=for heterogeneity across categories of each physical activity

Table 5. Relative risks (RR) and 95% group specific confidence intervals (gsCI) of incident vascular diseases, in women, in relation to various physical activities[d], reported at 3-year resurvey

	CORONARY HEART DISEASE			CEREBROVASCULAR DISEASE			VENOUS THROMBOEMBOLISM		
	Incident cases	**Minimally adjusted[a]**	**Fully adjusted[b] RR (95% gsCI[c])**	**Incident cases**	**Minimally adjusted[a]**	**Fully adjusted[b] RR (95% gsCI[c])**	**Incident cases**	**Minimally adjusted[a]**	**Fully adjusted[b] RR (95% gsCI[c])**
Walking									
Up to 1 hour per week	5940	1.00	1.00 (0.97 – 1.03)	2080	1.00	1.00 (0.96 – 1.04)	1770	1.00	1.00 (0.95 – 1.05)
> 1 - 5 hours per week	8500	0.80	0.87 (0.85 – 0.89)	2901	0.78	0.83 (0.80 – 0.86)	2376	0.75	0.81 (0.78 – 0.85)
> 5 hours per week	5768	0.79	0.86 (0.83 – 0.88)	1834	0.71	0.75 (0.72 – 0.79)	1621	0.75	0.83 (0.79 – 0.87)
$P_{heterogeneity}$			< 0.001			< 0.001			< 0.001
Gardening									
0 hours per week	5306	1.00	1.00 (0.97 – 1.03)	1848	1.00	1.00 (0.95 – 1.05)	1523	1.00	1.00 (0.95 – 1.05)
Up to 2 hours per week	6476	0.81	0.87 (0.85 – 0.89)	2084	0.76	0.81 (0.78 – 0.85)	1848	0.78	0.85 (0.81 – 0.89)
> 2 hours per week	8426	0.81	0.86 (0.84 – 0.88)	2883	0.78	0.81 (0.78 – 0.84)	2396	0.77	0.84 (0.81 – 0.88)
$P_{heterogeneity}$			< 0.001			< 0.001			< 0.001
Cycling									
0 hours per week	18,600	1.00	1.00 (0.98 – 1.02)	6302	1.00	1.00 (0.97 – 1.03)	5263	1.00	1.00 (0.97 – 1.03)
Up to 2 hours per week	1098	0.76	0.84 (0.79 – 0.89)	337	0.72	0.78 (0.70 – 0.87)	316	0.75	0.83 (0.74 – 0.93)
> 2 hours per week	510	0.79	0.83 (0.76 – 0.91)	176	0.83	0.87 (0.75 – 1.01)	188	1.01	1.08 (0.94 – 1.25)
$P_{heterogeneity}$			< 0.001			< 0.001			0.002
Any strenuous activity									
0 hours per week	13,561	1.00	1.00 (0.98 – 1.02)	4626	1.00	1.00 (0.97 – 1.03)	3853	1.00	1.00 (0.97 – 1.03)
Up to 2 hours per week	3594	0.74	0.82 (0.80 – 0.85)	1219	0.76	0.84 (0.79 – 0.89)	1009	0.72	0.79 (0.74 – 0.84)
> 2 hours per week	3053	0.82	0.88 (0.85 – 0.92)	970	0.80	0.86 (0.80 – 0.91)	905	0.84	0.91 (0.85 - 0.97)
$P_{heterogeneity}$			< 0.001			< 0.001			< 0.001
Housework									
Up to 3 hour per week	2932	1.00	1.00 (0.96 – 1.04)	1082	1.00	1.00 (0.94 – 1.06)	909	1.00	1.00 (0.94 – 1.07)
> 3 – 10 hours per week	6005	0.91	0.93 (0.91 – 0.95)	2076	0.87	0.88 (0.84 –0.92)	1843	0.90	0.92 (0.88 – 0.96)
> 10 hours per week	11,271	1.03	1.01 (1.00 – 1.03)	3657	0.89	0.88 (0.85 – 0.91)	3015	0.89	0.89 (0.86 – 0.92)
$P_{heterogeneity}$			< 0.001			0.001			0.008
Excess MET-hours of activity									
0-40 per week	6269	1.00	1.00 (0.98 – 1.03)	2186	1.00	1.00 (0.96 – 1.04)	1864	1.00	1.00 (0.96 – 1.05)
> 40 – 80 per week	7835	0.89	0.92 (0.90 – 0.94)	2613	0.84	0.86 (0.83 –0.89)	2314	0.88	0.92 (0.89 – 0.96)
> 80 per week	6104	0.94	0.96 (0.93 – 0.98)	2016	0.89	0.88 (0.84 – 0.92)	1589	0.82	0.85 (0.81 – 0.90)

$P_{heterogeneity}$	< 0.001	< 0.001	< 0.001

[a]Stratified by SES and Region
[b]Adjusted for BMI-by-age, smoking-by-age, alcohol-by-age and stratified by SES and Region
[c]gsCI=group specific confidence interval for RR
[d]An average of 9 years (median 9 years; interquartile range 8-11) follow-up per woman

Figure Legend:

Figure 1. Absolute risks and 95% group specific confidence intervals (gsCI) for incident vascular diseases, by strenuous and any physical activity, excluding the first 4 years of follow-up.